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# Nodular Regenerative Hyperplasia of the Liver: Description of Two Cases

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Nodular regenerative hyperplasia (NRH) of the liver is a condition of unknown origin, rarely occurring in children, usually accidentally discovered, described in association with a variety of clinical conditions and drugs. Confusion with other types of hepatic masses may pose a problem and for this reason NRH is considered a "tumor-like lesion." Histologically it consists of single or multiple regenerative foci. Hepatic failure and rupture of the liver have been rarely described as complications in adults, and not in children, and malignant transformation has not been demonstrated. Neither surgical removal nor other treatment is needed. These features are described as they were found in two patients we encountered. 

**Key words:** nodular regenerative hyperplasia, liver tumors in childhood, hepatic pseudoneoplastic lesions

## INTRODUCTION

Nodular regenerative hyperplasia (NRH) is a rare condition. It is characterized by the presence in the liver of parenchymal nodules, composed of cells resembling normal hepatocytes, and not associated with fibrosis. It occurs more often in adults than in children and it is usually an incidental discovery. It has been found in association with collagen diseases, congestive heart failure, hematologic abnormalities, metabolic disorders, neoplasms and a wide variety of drugs [3,11,17], but the origin remains unknown. The clinical and radiological differential diagnosis is often difficult, since NRH can mimic the findings in patients with hepatic neoplasms.

We present two cases of NRH, observed during the last three years in the Surgical Division of the Department of Pediatrics in Padua. Our purpose is to call attention to the entity, to emphasize the importance of adequate biopsy, and to discuss methods of management.

## CASE 1

M.F., a white male newborn, underwent complete excision of a mature sacrococcygeal teratoma soon after birth. No other treatment was carried out. Seven years later, hyperechoic lesions in the 2nd, 3rd, 6th and 7th hepatic segments were encountered as incidental findings during a routine follow-up abdominal ultrasonography (US) (Fig. 1). The nodules, which measured 0.5 to 4 cm in diameter, appeared as hypointense, poorly enhancing areas on computed tomography (CT). Recent history, clinical findings and liver function tests were unremarkable and the serum alpha-feto protein (AFP) concentration was within normal limits. Tumor recurrence was suspected so that, after an inconclusive echoguided fine needle biopsy, the child underwent laparotomy. Macroscopically, the liver appeared normal and multiple biopsies were taken in areas suspected of being abnormal. Histological examination was in favor of NRH. No resections were performed and presently all lesions are stable 3 years after diagnosis.

## CASE 2

S.R., an 8-year-old white female, had an abdominal US because of recurrent abdominal pain. It demonstrated the presence in the liver (5th and 6th segments) of multiple hyperechogenic, hypovascular masses, measuring 6 × 6 cm in diameter (Fig. 2). The child was in good condition and, as in the other case, her history, clinical findings, liver function tests and AFP were negative. CT scan and magnetic resonance imaging (MRI) confirmed the US findings, revealing hyperintense masses involving an hepatic area, 10 cm wide (Fig. 3). At diagnostic lap-

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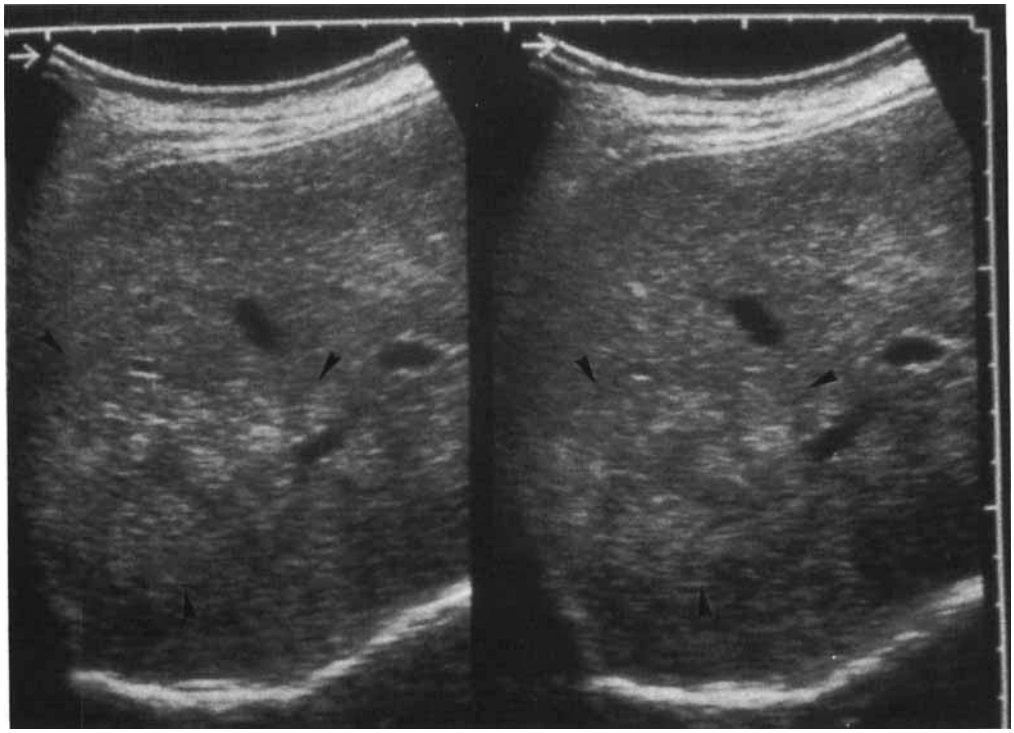


**Fig. 1.** Hepatic US. Multiple hyperechogenic nodules of varying size are scattered throughout liver parenchyma.

arotomy, the liver surface appeared normal, and intraoperative US was needed for guidance to the biopsy sites. The lesion was a NRH (Figs. 4,5). The patient did not receive any further treatment and presently is well without evidence of progression 2 years after diagnosis.

## DISCUSSION

NRH, also known as nodular transformation, nodular noncirrhotic liver, and miliary hepatocellular adenomatosis, is a condition characterized by the presence of diffuse regenerative nodules in the liver.

First described by Steiner in 1959 [1], it is relatively rare and usually found in adults. The largest pediatric series (16 cases) was gathered from the files of the Armed Forces Institute of Pathology and reported in 1991 [2].

The etiology is unclear. A variety of systemic diseases have been found to be associated: collagen diseases, congestive heart failure, rheumatoid arthritis, neoplasms and haematological disorders (polycythemia, multiple myeloma, chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma) [3,11,17]. Reported cases in the pediatric age group have been associated with Krabbe disease [12], portal hypertension [13,14], Wilms' tumor [15], and Down's syndrome [16]. Many authors [9,18–21] in their reports have emphasised the possible etiopathogenetic role of drugs administered in those diseases. These include corticosteroids (particularly anabolic steroids), phenobarbital, anti-cancer chemotherapeutic agents, immunosoppressive drugs, oral contraceptives and alcohol. Vascular and immunologic processes have also been considered. Vasculitis or vascular obstruction can lead to atrophy of the hepatic acini and consequent compensatory hyperplasia of those adjoining [1,9, 17,22,23]. In 1990, Wanless [24] concluded that NRH is a secondary and nonspecific tissue adaptation to aberrant distribution of blood flow and does no represent a specific entity.

The histological findings of NRH are characteristic [2,9,23,28]. There is a distortion of the lobular architecture by bulging nodules of hepatocytes, which may be periportal or eccentric in location, without fibrosis. Reticulum stain better delineates the hyperplastic foci, showing a typical condensation of reticular fibres around the proliferative nodules, due to the compression of the adjacent hepatocellular lamina. In some reports, marked hepatocellular dysplasia has been noted [9,23], but it is unusual and not found in our cases. Fibrosis and hepatocellular damage are minimal or not present.

Patients with NRH may be asymptomatic or may present with symptoms of portal hypertension [2,23] which could be related to compression of the portal vein at the hepatic hilum, or intraparenchymal venules and/or sinusoids by NRH nodules [9,23]. The two patients re-

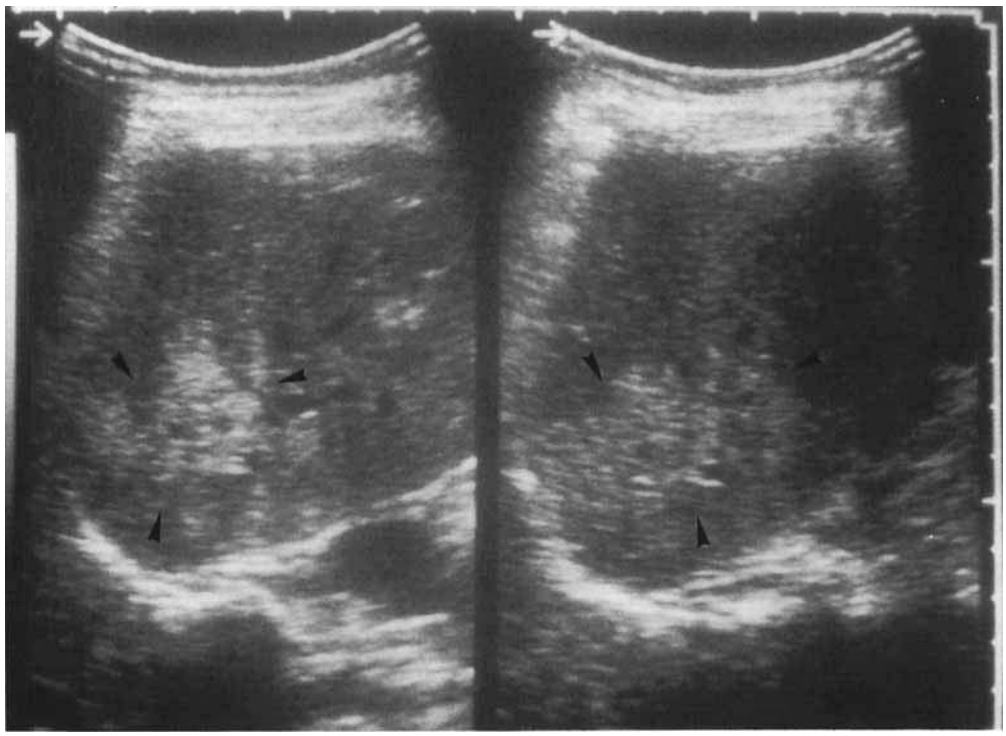


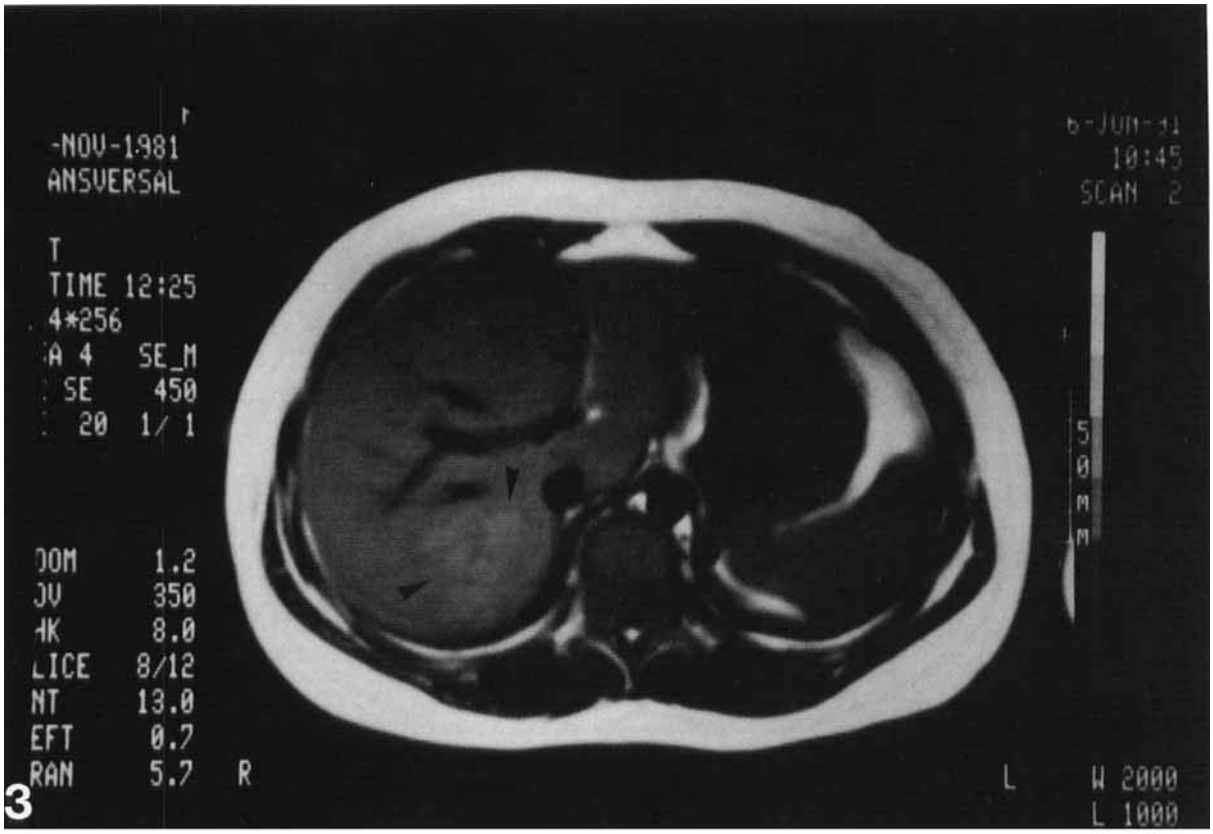
**Fig. 2.** Hepatic US. A large hyperechogenic area appears in the right lobe.

ported by Moran et al. [2], who had splenomegaly associated with portal hypertension, underwent portocaval and mesocaval shunts for bleeding varices. In one of them, the diagnosis of NRH was made during the operation. Both patients were relieved of symptoms postoperatively. Subsequent biopsies confirmed the presence of NRH, suggesting that the liver transformation is an irreversible condition. In another case of portal hypertension [13] the NRH was diagnosed during a minilaparotomy performed in a 14-year-old boy, who presented with splenomegaly and epistaxis. A previous laparoscopy had shown multiple nodules in the liver but the percutaneous Menghini biopsy specimens showed normal parenchyma and architecture. This boy's condition has remained unchanged during the ensuing 12 months of follow-up. Sometimes the NRH is found incidentally on physical examination or CT, laparotomy or autopsy performed for problems not related to the liver. Chandra in 1983 [15] described the case of a 12-year-old boy with Wilms tumor, in whom the NRH was discovered during exploratory surgery after preoperative chemotherapy and radiotherapy. Moran et al. found that in 4 out of 5 patients in whom NRH was discovered postmortem, the child died because of associated conditions. The cause of death in the fifth patient is not known [2].

NRH was an incidental finding during abdominal US in our 2 patients. Both children were healthy. Only one of them was suffering from abdominal recurrent pain for 3 months. The other patient was operated at birth for a mature sacro-coccygeal teratoma, but no further therapy was administered and no sequelae were present 8 years after.

The radiologic appearance of NRH is characteristic of a hepatic mass and for this reason NRH is considered a "tumor-like lesion." Hyperechogenic or isoechoic masses have been seen on US, with occasional anechoic centers corresponding to hemorrhagic foci, within the nodules. On CT scans, the nodules appear as hypointense, poorly enhancing areas, occasionally associated with hyperdense masses representing hemorrhage. US and CT may be normal when the nodules are microscopic in size while scintigraphy may reveal a patchy uptake of the radionuclide within the liver [23].

Dachmann et al. [23] have discussed the differential diagnosis when multiple liver nodules are present. NRH and metastases should be considered, as well as focal nodular hyperplasia (FNH), cirrhosis and tumors (hepatocellular adenoma, hepatocellular carcinoma, sarcoma). These entities all may have the same general appearance [25–27] but some details can suggest the diagnosis. In FNH, the masses are isoechoic to the rest of the liver [22] and a stellate central scar is usually present. Metastases are characterized by enhancement and are usually not incidental findings. Hepatic adenoma is usually a well defined single mass found in young women using oral contraceptives, while cirrhosis is characterized by dense fibrous bands between the nodules and cholestasis.



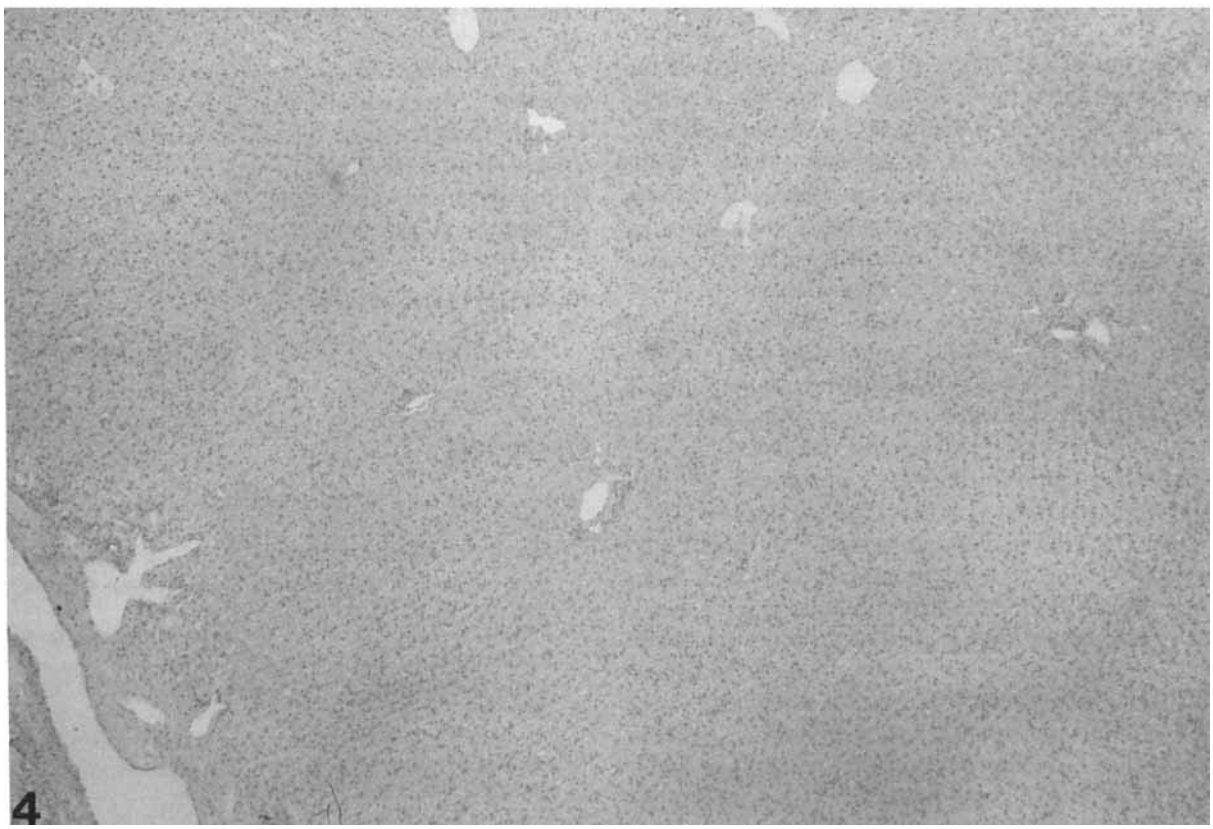




**Fig. 3.** CT scan. The hepatic CT scan shows multiple hyperintense hepatic nodules.
**Fig. 4.** Histology. The histological finding shows nodular architecture of the liver parenchyma.

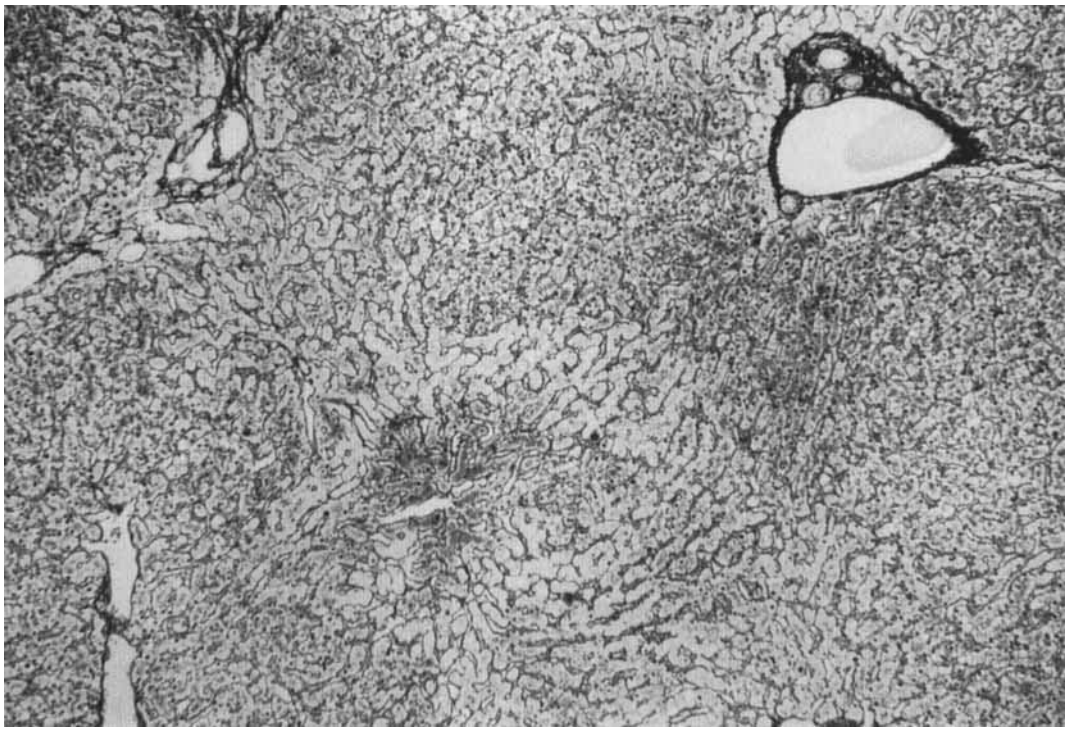


**Fig. 5.** Histology. Nodules of hyperplastic hepatocite distort the parenchyma. The reticulum stain shows a typical condensation of reticular fibres around the proliferative nodules.

Despite the greatly increased accuracy of modern imaging methods, none of them singly or together is able to differentiate NRH from a malignancy with certainty, and histologic confirmation is mandatory. Many reports [9,13,15] emphasize the need of an open wedge biopsy because insufficient tissue for diagnosis is obtained by needle biopsies [3,7,8]. This was the case in our patient 1, who underwent US-guided needle biopsy before laparotomy, with inconclusive results. The diagnosis of NRH was made only after adequate tissue was provided by open biopsy. We would like to stress the importance of US guidance in obtaining accurate samples. In our case 2, the liver surface appeared normal at laparotomy, and only blind and therefore perhaps inconclusive biopsies would have been obtained without the assistance of US.

Even though NRH is not reversible [2], the nodules do not seem to have a tendency to increase in size or number, and remain dormant. This has been true of our 2 patients, who remain well 2 and 3 years after diagnosis. US and CT scans obtained every 6 months do not show any change in the size and features of the nodules.

Some complications, such as hepatic failure and rupture of the liver, have been described in adults but not in children. Finally, malignant transformation has been observed only in experimental models [9]. For these reasons, in our opinion, surgical resection, even if feasible, is not mandatory. A close follow-up is always necessary.

In conclusion, awareness of the existence of NRH is important, along with its clinical, radiological and histological characteristics. NRH can then be considered in the differential diagnosis of nodular hepatic lesions and biopsy proof can allow the correct, nonaggressive management to be instituted.

## ACKNOWLEDGMENTS

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